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Impact of Anticholinergic Burden on Cognitive Performance: A Cohort Study of Community-Dwelling Older Adults

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Abstract:	Objectives: The objective of this cross-sectional study was to assess with adequate confounding control, whether anticholinergic burden affects cognitive performance in community-dwelling older adults. Design: Prospectively collected International Residential Assessment Instrument-Home Care (interRAI-HC) assessment data. Settings and Participants: Community-dwelling people in New Zealand aged ≥65 years who have undergone a standardized needs assessment between June 2012 and June 2014 using the interRAI-HC, and who provided consent were included. The dose calculation from the drug burden index score was applied to a list of Drugs with Anticholinergic Properties (DAP) to quantify anticholinergic burden (DAP-DBI), and the Cognitive Performance Scale to assess cognitive function. The outcome is the severity of cognitive impairment determined at the first interRAI-HC assessment as an ordinal-categorical variable, the severity categories, from the best to the worst are “None”, “Mild”, “Moderate” and “Severe”. The probability used for the inverse weight is the probability of non-zero anticholinergic burden (DAP-DBI>0). We constructed an ordinal regression model based on various demographic, social and clinical characteristics to assess whether anticholinergic burden affects cognitive performance, in the sample weighted by the inverse probability of treatment weight (IPTW). Results: 14,198 individuals received 31994 interRAI assessments. After IPTW adjustment, baseline characteristics in both groups were balanced (population standardized bias < 0.20). The ITPW-adjusted ordinal regression model showed a significant association of poor cognitive performance with anticholinergic burden. Odds ratio = 2.53 (95%CI, 1.93-3.31) for DAP-DBI between 0.1 and 0.99, OR = 1.51 (95%CI, 1.14-1.20) for DAP-DBI between 1 and 2.5, and OR = 2.89 (95%CI, 2.18, 3.84) for DAP-DBI above 2.5), comparing to those with zero DAP-DBI. Conclusions and Implications: In older adults requiring complex care anticholinergic burden was associated with poor cognitive performance. Anticholinergic burden is a modifiable risk factor and should be routinely monitored during geriatric risk assessments and reduced whenever feasible.

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To: Dr Sheryl Zimmerman and Dr Philip Sloane
Editor-in-chief
Journal of Post-Acute and Long-Term Care Medicine (JAMDA)
C/o Elsevier
Amsterdam
Netherlands

Dear Dr Sheryl Zimmerman and Dr Philip Sloane,

On behalf of my co-authors, I would like to submit the following manuscript for your consideration:

Impact of Anticholinergic Burden on Cognitive Performance: A Cohort Study of Community-Dwelling Older Adults

This paper has not been published or accepted for publication nor has been published in whole or part elsewhere. I attest to the fact that all authors listed on the title page have read the manuscript, agree to the validity and legitimacy of the data and its interpretation, and agree to its submission.

We believe this paper may be suitable to be published in your journal addressing emerging clinical issues relevant to health in older adults. Our study found in older adults requiring complex care anticholinergic burden was associated with poor cognitive performance . Given the use of anticholinergic drugs in older people is a public health concern, the study findings are important for both New Zealand and international researchers.

I hope the reviewing process finds the manuscript acceptable for publication in your journal and I look forward to hearing the outcome of the peer review. If I can provide any additional information, please contact me at p.nishtala@bath.ac.uk

Sincerely,
Prasad S Nishtala PhD

Impact of Anticholinergic Burden on Cognitive Performance: A Cohort Study of Community-Dwelling Older Adults

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Running Title: Impact of Anticholinergic Burden on Cognitive Performance

ABSTRACT

Objectives: The objective of this cross-sectional study was to assess with adequate confounding control, whether anticholinergic burden affects cognitive performance in community-dwelling older adults.

Design: Prospectively collected International Residential Assessment Instrument- Home Care (interRAI-HC) assessment data.

Settings and Participants: Community-dwelling people in New Zealand aged ≥65 years who have undergone a standardized needs assessment between June 2012 and June 2014 using the interRAI-HC, and who provided consent were included. The dose calculation from the drug burden index score was applied to a list of Drugs with Anticholinergic Properties (DAP) to quantify anticholinergic burden (DAP-DBI), and the Cognitive Performance Scale to assess cognitive function. The outcome is the severity of cognitive impairment determined at the first interRAI-HC assessment as an ordinal-categorical variable, the severity categories, from the best to the worst are "None", "Mild", "Moderate" and "Severe". The probability used for the inverse weight is the probability of non-zero anticholinergic burden (DAP-DBI>0). We constructed an ordinal regression model based on various demographic, social and clinical characteristics to assess whether anticholinergic burden affects cognitive performance, in the sample weighted by the inverse probability of treatment weight (IPTW).

Results: 14,198 individuals received 31994 interRAI assessments. After IPTW adjustment, baseline characteristics in both groups were balanced (population standardized bias < 0.20). The ITPW-adjusted ordinal regression model showed a significant association of poor cognitive performance with anticholinergic burden. Odds ratio = 2.53 (95%CI, 1.93-3.31) for DAP-DBI between 0.1 and 0.99, OR = 1.51 (95%CI, 1.14-1.20) for DAP-DBI between 1 and

2.5, and OR = 2.89 (95%CI, 2.18, 3.84) for DAP-DBI above 2.5), comparing to those with zero DAP-DBI.

Conclusions and Implications: In older adults requiring complex care anticholinergic burden was associated with poor cognitive performance. Anticholinergic burden is a modifiable risk factor and should be routinely monitored during geriatric risk assessments and reduced whenever feasible.

Introduction

Older people are particularly susceptible to the adverse effects of anticholinergic burden due to advanced age, polypharmacy (≥5 drugs), comorbidities, increased permeability of the blood-brain barrier, diminished cholinergic reserves in the brain and pharmacokinetic and pharmacodynamic alterations slowing drug metabolism and drug clearance [1-7].

Anticholinergic burden increases the risk of cognitive impairment in older people [8]. A recent nested case-control study (N= 284,343) conducted in the United Kingdom examined the association between anticholinergic burden and risk of dementia [9]. This observational study accounted for several important confounders identified as risk factors for dementia and addressed the risk of protopathic bias by excluding anticholinergic exposures well before the date of incident dementia diagnosis. However, the study did not adjust for the baseline differences in the clinical characteristics in the case and control groups and for time-dependent exposures, and both factors can threaten the validity of the results. A systematic review of the literature conducted by Kersten et al. reported mixed associations between high anticholinergic burden and cognitive performance in older people [10]. Observational studies included in this systematic review were either cross-sectional or cohort designed, and nine of the studies found no association between anticholinergic burden and cognitive performance. However, a meta-analysis of 18 studies comprising of prospective cohorts (n = 10), retrospective cohorts (n = 4),

case-control (n = 2), and randomized control trials (n = 2) reported that exposure to anticholinergic burden is associated with an increased risk of cognitive impairment in older people [8].

Non-randomized studies are likely to provide biased estimates of treatment effects as the treated and untreated groups may have systematic differences in covariates that may influence the study outcomes [11]. The inverse treatment probability weight (IPTW) method provides an adjusted exposure effect and mitigates confounding by eliminating the strong influence of such covariates on the drug exposure [12].

This study takes advantage of the international residential assessment instrument (interRAI) dataset. It was created by an international panel of clinicians and academics and is used in over 30 countries [13]. There have been several studies presenting that the data is reliable. New Zealand is one of the first countries in the world to mandate the use of the interRAI for all people who have complex needs.

The overarching objective of this study was to examine the association between anticholinergic burden and cognitive function in community-dwelling older adults.

Methods

Study design

In this cross-sectional study, we included community-dwelling adults aged ≥65 years with interRAI Home Care Assessment System (interRAI-HC) assessment undertaken between 1 June 2012 and 30 June 2014. The interRAI-HC data has been used extensively for examining health outcomes in the population of older adults in NZ [14]. This study was approved by the Ministry of Health's Health and Disability Health Committees (ref 15/CEN/45) and only includes individuals consented for their anonymised data to be used for research purposes.

The interRAI–HC assessment includes 236 questions over 20 distinct domains covering demographic, clinical, social, psychosocial and environmental assessments. The interRAI-HC instrument has been described in detail elsewhere [14, 15]. The data is of good quality and readily linked with other data sets. All interRAI assessors complete a three-day training programme. The 1.5-hour interRAI assessment includes 236 standardized items which are recorded electronically, and all data is stored nationally (14).

Anticholinergic burden

We used the reference composite anticholinergic scale derived from a systematic review of the literature examining anticholinergic burden in older adults to identify drugs with anticholinergic properties (DAPs) [16]. We linked prescription data from the PHARMAC database with interRAI assessments using the NZ national unique identifier (National Health Index or NHI) number. We extracted details of prescriptions and their doses for the included anticholinergic drugs 90 days before the assessment date and the drug burden attributable to each anticholinergic medication was calculated using the equation, Drug Burden Anticholinergic Index (DBI (ACh)) =D/(D+ δ); where D is the daily dose in milligrams taken by the individual, and δ is the minimum efficacious dose [17]. To obtain the daily dose we divided the product of quantity dispensed and weight by 90 days. The anticholinergic burden was calculated by summing up the DBI (ACh) for each DAP dispensed to the participant. This measure of exposure differs from the anticholinergic component of the validated DBI [18] as the validated DBI only includes drugs with clinical anticholinergic effects documented on the registered product information, while the DAP list includes a wider list of drugs with possible anticholinergic effects. We only considered oral dosage forms and transdermal fentanyl but excluded all other formulations for calculation of anticholinergic burden. Oxybutynin transdermal patch is not funded by PHARMAC and hence not included in the analyses.

We measured anticholinergic burden within 90 days before the first interRAI-HC assessment, and the anticholinergic burden was summarized into four possible categories, DAP-DBI = 0, >0 and ≤1, >1 and ≤2.5, and >2.5.

Cognitive performance

All participants undertaking an interRAI-HC assessment have their cognition assessed using the Cognitive Performance Scale (CPS). The CPS assessment pools information on memory impairment, consciousness, and executive function, with scores ranging from 0 (intact) to 6 (very severe impairment). Several validation studies have found the scores derived from the CPS to be highly correlated with the Mini-Mental State Examination (MMSE) scores [19, 20]. For this study, we categorised individuals into four categories: CPS score 0 and 1-No cognitive impairment, 2-mild cognitive impairment, 3-moderate and CPS score >4 with severe cognitive impairment. Previous studies have used a cut-off of 2 points or more to define cognitive performance and used similar categorizations to define higher degrees of cognitive impairment [19, 21, 22].

Covariates variables

The covariates included in the model were demographic characteristics (age in years, sex, marital status, living status), social characteristics (alcohol consumption, smoking status), clinical characteristics (chronic obstructive pulmonary disease, coronary heart disease, diabetes, stroke, hearing impairment and visual impairment), and self-reported functional characteristics (activities of daily living, instrumental activities of daily living, falls history). We chose these variables *a priori* because of their potential association with anticholinergic exposure.

Outcome

The outcome variable is the severity of cognition impairment determined using the CPS at the first interRAI assessment as an ordinal-categorical variable, the severity categories, from the best to the worst are “None” (i.e. normal), “Mild”, “Moderate” and “Severe”.

Inverse probability treatment weighting

For ITPW, the probability used for the inverse weight is the probability of having a DAP-DBI of 0, between 0 and 1 (excluding 0), between 1 and 2.5 (excluding 1), and above 2.5, within 90 days before the first interRAI assessment. We fitted a multinomial logistic model to calculate the above-mentioned probabilities for each individual. We included all covariates in the multinomial logistic regression model.

We checked that covariates are balanced between the 4 DAP-DBI categories after ITPW, so that we can be confident that spurious effects of covariates on exposures are sufficiently reduced by computing the “population standardized bias” (PSB) for each variable and for each DAP-DBI category as described by McCaffrey et al [23]. The covariates are sufficiently balanced if all PSBs are no higher 0.20. (**Figure 1**)

Ordinal regression

We calculated the odds ratio of having a worse cognitive impairment due to DAP-DBI exposure by ordinal regression with and without ITPW weighting. The outcome of interest is the severity of cognitive impairment of an individual, which was coded as an ordinal-categorical variable (from 0 for normal cognition, to 3 for severe impairment). We used the function "polr" in the R package "MASS" for the ordinal regression model.

Results

We derived the final study cohort (N=14,198) from the interRAI-HC information available for 105,502 assessments for 70,159 individuals (**Flow chart**). The mean age (SD) of the cohort was 82.5 years (7.2), 8,866 (62.4%) were female, and the majority, 12,712 (89.5%), were European (**Table 1**).

The study cohort included 14,198 individuals who received 31994 assessments. Among the study cohort, majority (n = 8148, 57.4%) had no cognitive impairment at baseline, 31.7% (n = 4503) had mild cognitive impairment, 7.3% (n = 1033) had moderate cognitive impairment, and a very low proportion (n = 514, 3.6%) had severe cognitive impairment (**Flow chart**).

Demographic, social and clinical characteristics of the study population are shown in **Table 1.** Before covariate balancing, persons with anticholinergic exposure had more comorbidities including chronic obstructive pulmonary disease, congestive heart failure, coronary heart disease, depression, diabetes, and were fatigued with reduced mobility and recent hospitalisations. After ITPW adjustment, baseline characteristics were balanced (population standardized bias < 0.20 for all variables and in all DAP-DBI categories (**Figure 1**)

The IPTW-adjusted ordinal regression model showed a significant association between cognitive performance and anticholinergic exposure. With a DAP-DBI > 2.5, the odds of having a worse cognitive outcome is approximately 2.9 times higher (OR = 2.89 (95% CI 2.18-3.84 with ITPW)) relative to zero DAP-DBI. Significant association of worse cognitive outcome and non-zero DAP-DBI were also observed for lower DAP-DBI ranges, with and without ITPW (**Figure 2**).

Discussion

This study found an association between anticholinergic exposure and cognitive performance in a population of older adults requiring complex care. The study findings are consistent with two large cohort studies that have examined an association with anticholinergic burden and

poor cognitive performance [24, 25]. In a large cohort of 13,004 participants aged 65 and older living in England and Wales the use of drugs with definite anticholinergic activity was associated with a 0.33□point greater decline in MMSE scores (95% CI, 0.03–0.64) [24]. The PAQUID cohort study involving 1780 community-dwelling participants aged 70 and older living in South Western France reported that short-term exposure to DAPs for 2-weeks was associated with low MMSE scores (OR = 1.4; 95% CI 1.0, 2.1) [25]. Similarly, a cohort study conducted among 372 older adults living in France reported that use of DAPs for more than 1 year was a strong predictor of mild cognitive impairment (odds ratio 5.12, P = 0.001) [26]. Similar findings were echoed by Han et al., among 504 community-dwelling men, a 1-unit increase in the total anticholinergic burden per 3 months was associated with a 0.32-point (95% confidence interval (CI)= 0.05-0.58) decrease in short-term memory measured using the Hopkins Verbal Recall Test [27].

More recently, two longitudinal studies conducted in the United Kingdom reported a dose-response relationship between anticholinergic burden and risk of dementia in older adults after controlling for risk factors for dementia [9, 28]. The hazard ratios for the risk of dementia in each study were 1.49 (95% CI, 1.44-1.54) [9] and 1.11 (95% CI, 1.08 to 1.14) [28], respectively. We cannot directly compare the findings of our study with these two large observational studies because of the differences in the study population, dissimilarities in the quantification of anticholinergic burden and importantly these studies examined incident dementia as their study outcome.

In comparison to previous cohort studies, a methodological improvement of the current study is the use of the IPTW method to diminish bias due to confounding factors that dictate exposures, resulting in imbalanced distribution of baseline characteristics across exposure groups. Our study has several other strengths, including its large size, unique population

characteristics, nationwide coverage in NZ, and use of an internationally recognized standardized instrument for geriatric risk assessment. Another notable strength of our study is that we used a validated pharmacological model-the drug burden index- to quantify the anticholinergic burden [18]. Previous studies that examined association of cumulative anticholinergic use on cognitive performance lacked information about the dose and duration of anticholinergic use [24, 26, 29, 30]. We accounted for several comorbidities associated with DAP use in the multinomial logistic regression model for deriving the IPTW, thus to an extent mitigating confounding by indication.

Our study noted some important limitations. We did not ascertain if individuals prescribed DAPs have taken them, nor did we account for over-the-counter DAPs, as these could lead to exposure misclassification. Given there is a lack of international consensus and poor concordance of currently used scales to measure anticholinergic burden, we used the reference composite scale which identified DAPs from already published rating scales used in clinical research to quantify anticholinergic burden. The reference composite scale identifies isosorbide, metoprolol, metformin, furosemide warfarin, and digoxin as DAPs. These drugs are not included in the validated DBI, and maybe appropriate therapies for the treatment of coronary heart disease, congestive heart failure, diabetes and stroke which are all risk factors for cognitive impairment. The prevalence of a high DAP-DBI> 2.5 exposure is greater than that seen in studies of the validated DBI because a much broader range of drugs were defined as anticholinergic in the DAP measure. The lack of dose-response seen with the relationship between DAP-DBI and cognitive impairment suggests that this measure of anticholinergic burden is not strongly associated with cognitive impairment, and a focus on anticholinergic drugs that cross the blood brain barrier may be appropriate to investigate in future studies. Another possible explanation for this finding is that anticholinergic drugs may be deprescribed

in people living with severe cognitive impairment, consistent with studies that reported decreased use of PIMs in people living with dementia.

We calculated anticholinergic burden before the first and second geriatric risk assessments but not for the entire study period. However, a previous epidemiological study conducted on the same interRAI-HC cohort found that the drug burden as a time-varying covariate did not change substantially over the study period [31]. Kashyap et al. highlighted critical methodological challenges faced in observational studies examining anticholinergic burden and cognitive decline [32]. Studies that have reported a raw change in MMSE scores have found a negative association [24], while studies that used a clinical definition of cognitive change were less likely to find associations with anticholinergic exposure [29]. Although several validation studies have found that the CPS to be highly correlated with the MMSE scores, it is possible that categorization of CPS scores in our study may have misclassified the cognitive status of the study participants. Another limitation of our study is that we followed our cohort for two years, and longer duration studies may be required to determine the potential long-term impact of anticholinergic burden on cognitive performance. Despite confounding control, this observational study only shows associations and the findings do not infer causality.

Conclusions

In older New Zealanders requiring complex care high anticholinergic burden was associated with poor cognitive performance. Anticholinergic burden is a modifiable risk factor and should be routinely monitored during geriatric risk assessments and reduced whenever feasible.

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Author contributions

PN, HA, LH and TC contributed to data analysis, data interpretation, and writing of the manuscript; SH and HJ contributed to data interpretation and reviewing the manuscript.

Conflicts of interest

No authors had conflicts of interest to declare.

Table 1 Baseline characteristics of 14,198 study participants stratified by anticholinergic exposures

Variable	Unexposed =2464 n (%)	DAP-DBI 0-0.99 =7708 n (%)	DAP-DBI 1-2.5 =3744 n (%)	DAP-DBI >2.5 =282 n (%)
Age group				
65-74	319 (12.9)	1084 (14.0)	655 (17.5)	66 (23.4)
75-84	984 (39.9)	3188 (41.4)	1697 (45.3)	134 (47.5)
85-94	1032 (41.8)	3203 (41.6)	1312 (35.0)	80 (28.4)
95+	129 (5.2)	233 (3.0)	80 (2.2)	2 (0.7)
Gender				
Female	1542 (62.6)	4879 (63.3)	2264 (60.5)	181 (64.2)
Male	922 (37.4)	2829 (36.7)	1480 (39.5)	101 (35.8)
Ethnicity				
European	2161 (87.7)	6875 (89.2)	3405 (90.9)	271 (96.1)
Māori	106 (4.3)	360 (4.7)	160 (4.3)	3 (1.1)
Other	197 (8.0)	473 (6.1)	179 (4.8)	8 (2.8)
Marital status				
Married	2161 (87.7)	6882 (89.3)	3339 (89.2)	255 (90.4)
Other	303 (12.3)	826 (10.7)	405 (10.8)	27 (9.6)
Living status				
Alone	1250 (50.7)	3934 (51.0)	1801 (48.1)	126 (44.7)
Other	113 (4.6)	285 (3.7)	128 (3.4)	9 (3.2)
With child only	291 (11.8)	818 (10.6)	364 (9.7)	26 (9.2)
With non-relatives	26 (1.1)	66 (0.9)	32 (0.9)	1 (0.4)
With relative	69 (2.8)	171 (2.2)	59 (1.6)	4 (1.4)
With spouse and partner only	715 (29.0)	2434 (31.6)	1360 (36.3)	116 (41.1)
Bladder				
Continent	804 (32.6)	2922 (37.9)	1463 (39.1)	116 (41.1)
Incontinent	1660 (67.4)	4786 (62.1)	2281 (60.9)	166 (58.9)
Bowel				
Continent	296 (12.0)	969 (12.6)	465 (12.4)	43 (15.2)
Incontinent	2168 (88.0)	6739 (87.4)	3279 (87.6)	239 (84.8)
Body Mass Index				
Normal	702 (28.5)	1987 (25.8)	801 (21.4)	50 (17.7)
Obese	174 (7.1)	825 (10.7)	618 (16.5)	48 (17.0)
Overweight	387 (15.7)	1457 (18.9)	774 (20.7)	72 (25.5)
Underweight	109 (4.4)	348 (4.5)	122 (3.2)	6 (2.2)
Unknown	1092 (44.3)	3091 (40.1)	1429 (38.2)	106 (37.6)
Activities of daily living				
Dependent	66 (2.7)	164 (2.1)	69 (1.8)	12 (4.3)
Extensive	141 (5.7)	500 (6.5)	219 (5.8)	25 (8.9)
Independent	1681 (68.2)	5078 (65.9)	2610 (69.7)	190 (67.4)
Limited	195 (7.9)	775 (10.1)	359 (9.6)	19 (6.7)
Maximal	32 (1.3)	135 (1.8)	64 (1.7)	6 (2.1)
Supervision	349 (14.2)	1056 (13.7)	423 (11.3)	30 (10.6)

Instrumental activities of daily living				
0-16	808 (32.8)	2148 (27.9)	1148 (30.7)	84 (29.8)
17-28	683 (27.7)	2411 (31.3)	1251 (33.4)	94 (33.3)
29-38	574 (23.3)	1898 (24.6)	862 (23.0)	73 (25.9)
39+	399 (16.2)	1251 (16.2)	483 (12.9)	31 (11.0)
Alcohol consumption				
Non-drinker	1804 (73.2)	5945 (77.1)	2897 (77.4)	221 (78.4)
One or more drinks	660 (26.8)	1763 (22.9)	847 (22.6)	61 (21.6)
Smoking				
Non-smoker	2325 (94.4)	7359 (95.5)	3585 (95.8)	265 (94.0)
Smoker	139 (5.6)	349 (4.5)	159 (4.2)	17 (6.0)
Hearing impairment				
None	1293 (52.5)	3935 (51.0)	1988 (53.1)	156 (55.3)
Minimal	700 (28.4)	2348 (30.5)	1144 (30.6)	89 (31.6)
Moderate	471 (19.1)	1425 (18.5)	612 (16.3)	37 (13.1)
Vision impairment				
None	1773 (72.0)	5508 (71.5)	2713 (72.5)	211 (74.8)
Minimal	470 (19.1)	1486 (19.3)	703 (18.8)	56 (19.9)
Moderate	221 (8.9)	714 (9.2)	328 (8.7)	15 (5.3)
Depression				
Absent	2368 (96.1)	6748 (87.5)	3145 (84.0)	242 (85.8)
Present	96 (3.9)	960 (12.5)	599 (16.0)	40 (14.2)
Falls history				
None within the last 90 days	1588 (64.4)	4911 (63.7)	2302 (61.5)	180 (63.8)
Fell 31-90 days ago	281 (11.4)	906 (11.8)	430 (11.5)	30 (10.6)
One fall in the last 30 days	390 (15.8)	1147 (14.9)	619 (16.5)	43 (15.3)
Two or more in the last 30 days	205 (8.4)	744 (9.7)	393 (10.5)	29 (10.3)
Stroke				
None	2118 (86.0)	6357 (82.5)	3119 (83.3)	227 (80.5)
Diagnosed	346 (14.0)	1351 (17.5)	625 (16.7)	55 (19.5)
Chronic obstructive pulmonary disease				
None	2221 (90.1)	6699 (86.9)	3000 (80.1)	210 (74.5)
Diagnosed	243 (9.9)	1009 (13.1)	744 (19.9)	72 (25.5)
Cancer				
None	2237 (90.8)	6864 (89.1)	3286 (87.8)	244 (86.5)
Diagnosed	227 (9.2)	844 (10.9)	458 (12.2)	38 (13.5)
Congestive heart failure				
None	2328 (94.5)	6536 (84.8)	2827 (75.5)	193 (68.4)
Diagnosed	136 (5.5)	1172 (15.2)	917 (24.5)	89 (31.6)
Coronary heart disease				
None	2042 (82.9)	5318 (69.0)	2227 (59.5)	129 (45.7)
Diagnosed	422 (17.1)	2390 (31.0)	1517 (40.5)	153 (54.3)

Diabetes				
None	2213 (89.8)	6126 (79.5)	2774 (74.1)	192 (68.1)
Diagnosed	251 (10.2)	1582 (20.5)	970 (25.9)	90 (31.9)
Mobility				
1000+ meters	364 (14.8)	657 (8.5)	201 (5.4)	3 (1.1)
100+ meters	578 (23.5)	1507 (19.6)	630 (16.8)	33 (11.7)
50-99 meters	390 (15.8)	1331 (17.3)	634 (16.9)	48 (17.0)
5-49 meters	814 (33.0)	3070 (39.8)	1666 (44.5)	143 (50.7)
Less than 5 meters	212 (8.6)	786 (10.2)	464 (12.4)	38 (13.5)
Did not walk	106 (4.3)	357 (4.6)	149 (4.0)	17 (6.0)
Hospitalisation				
None within the last 90 days	1880 (76.3)	5050 (65.5)	2309 (61.7)	168 (59.6)
31-90 days ago	234 (9.5)	1072 (13.9)	578 (15.4)	50 (17.7)
In the last 30 days	203 (8.2)	915 (11.9)	523 (14.0)	38 (13.5)
Now in hospital	147 (6.0)	671(8.7)	334 (8.9)	26 (9.2)
Fatigue				
None	1090 (44.2)	2559 (33.2)	934 (24.9)	55 (19.5)
Minimal	881 (25.8)	2762 (35.8)	1336 (35.7)	87 (30.9)
Moderate	391 (15.9)	1776 (23.0)	1062 (28.4)	96 (34.0)
Severe	102 (4.1)	611 (7.9)	412 (11.0)	44 (15.6)

DAP-DBI (Drugs with Anticholinergic Properties-Drug Burden Index)

Flow chart

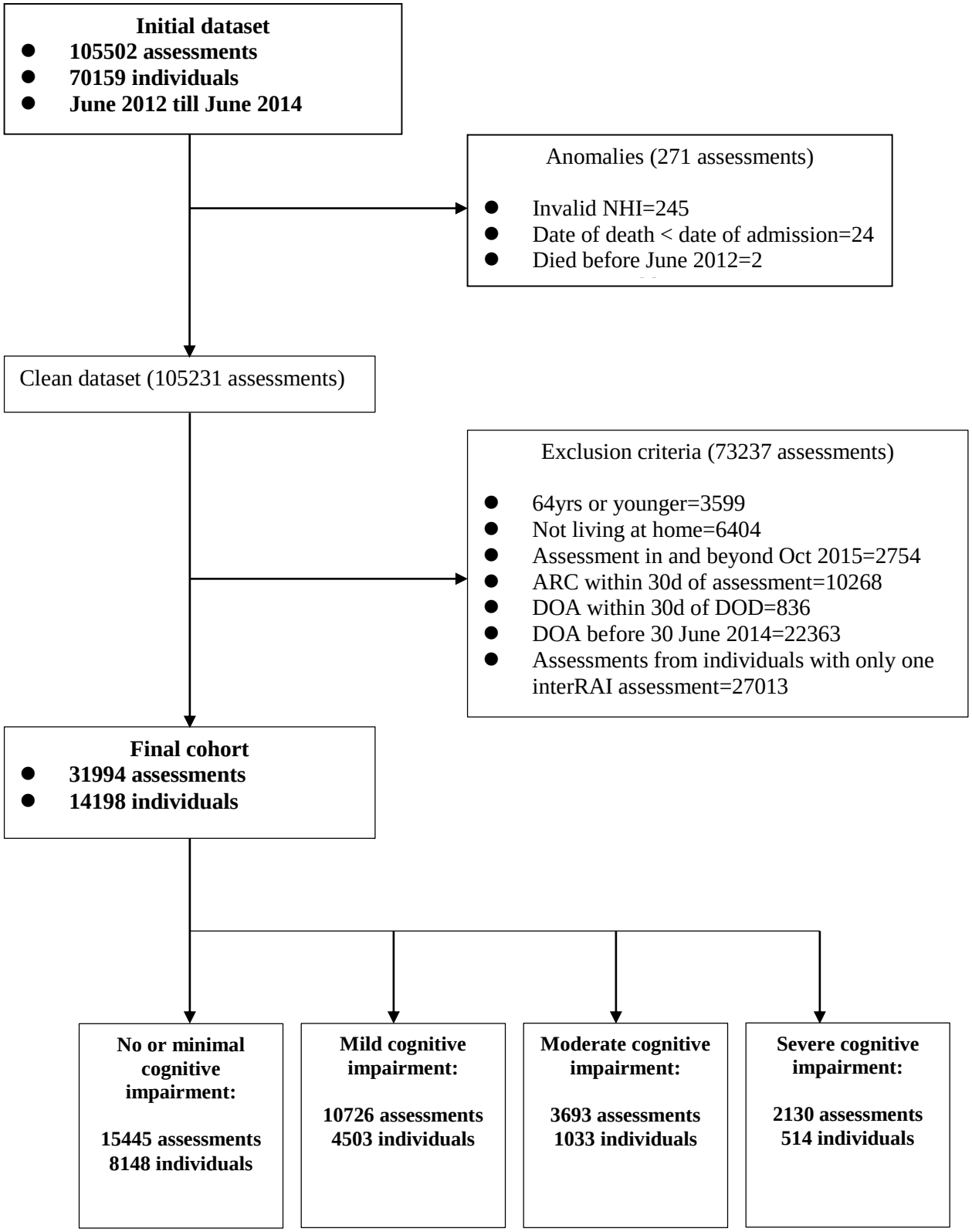
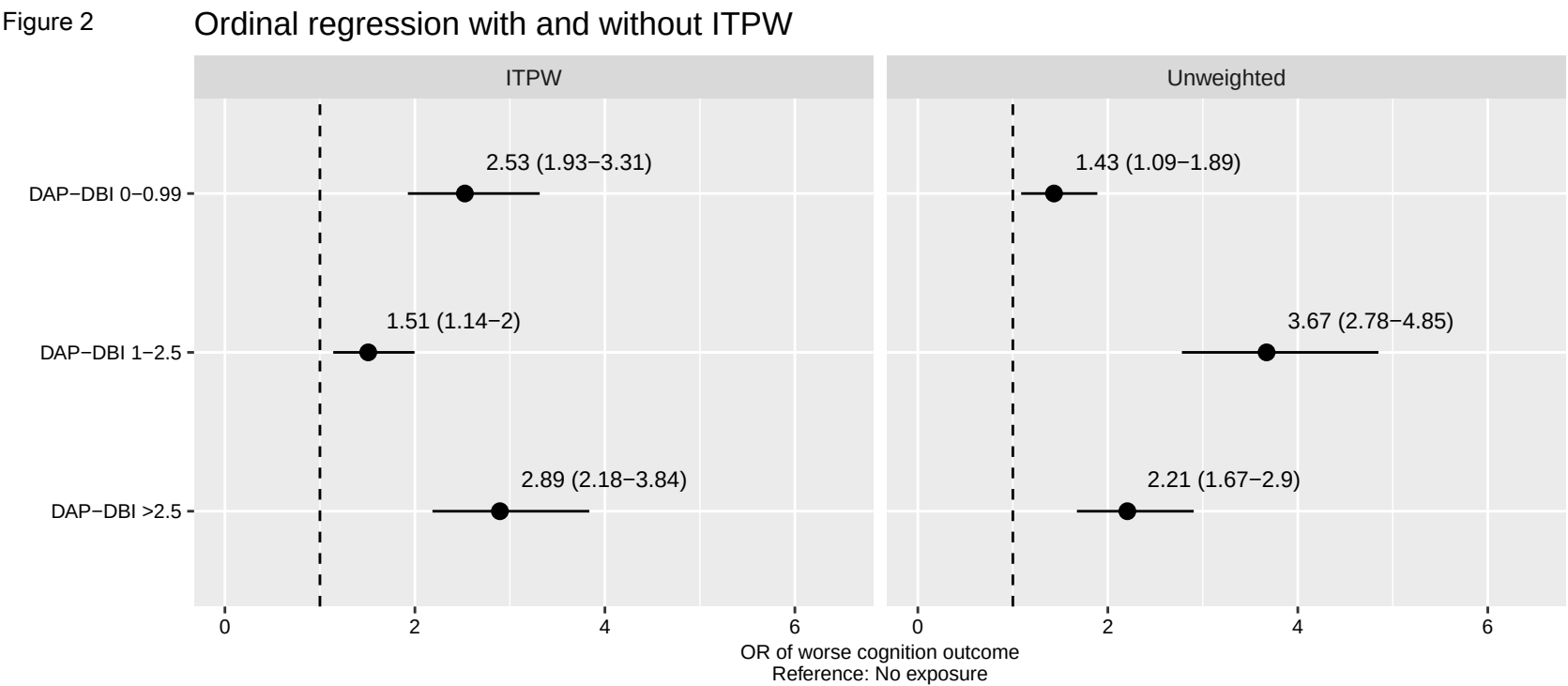

Initial dataset
105502 assessments
70159 individuals
June 2012 till June 2014
Anomalies (271 assessments)
Invalid NHI=245
Date of death < date of admission=24
Died before June 2012=2
Clean dataset (105231 assessments)
Exclusion criteria (73237 assessments)
64yrs or younger=3599
Not living at home=6404
Assessment in and beyond Oct 2015=2754
ARC within 30d of assessment=10268
DOA within 30d of DOD=836
DOA before 30 June 2014=22363
Assessments from individuals with only one interRAI assessment=27013
Final cohort
31994 assessments
14198 individuals
No or minimal cognitive impairment:
15445 assessments
8148 individuals
Mild cognitive impairment:
10726 assessments
4503 individuals
Moderate cognitive impairment:
3693 assessments
1033 individuals
Severe cognitive impairment:
2130 assessments
514 individuals

Figure 1


Covariate balance with and without ITPW
No exposure
DAP−DBI 0−0.99
DAP−DBI 1−2.5
DAP−DBI >2.5
Age group: 65−74
Age group: 75−84
Age group: 85−94
Age group: 95+
Gender: Female
Gender: Male
Ethnicity: European
Ethnicity: Maori
Ethnicity: Other
Marital state: Married
Marital state: Other
Residential state: Alone
Residential state: Other
Residential state: With child only
Residential state: With non−relatives
Residential state: With relatives
Residential state: With spouse and partner only
Bladder state: Continent
Bladder state: Out of control
Bowel state: Continent
Bowel state: Out of control
BMI category: Normal
BMI category: Obese
BMI category: Overweight
BMI category: Underweight
BMI category: Unknown
ADLH: Dependent
ADLH: Extensive
ADLH: Independent
ADLH: Limited
ADLH: Maximal
ADLH: Supervision
IADL: 0−16
IADL: 17−28
IADL: 29−38
IADL: 39+
Alcohol consumption: Non−drinker
Alcohol consumption: One or more drinks
Smoking: Non−smoker
Smoking: Smoker
Hearing impairment: None
Hearing impairment: Minimial
Hearing impairment: Moderate
Vision impairment: None
Vision impairment: Minimial
Vision impairment: Moderate
Depression: Absent
Depression: Present
Fall history: None within the last 90 days
Fall history: Fell 31−90 days ago
Fall history: One fall in the last 30 days
Fall history: Two or more in the last 30 days
Stroke: None
Stroke: Diagnosed
COPD: None
COPD: Diagnosed
Cancer: None
Cancer: Diagnosed
CHF: None
CHF: Diagnosed
CHD: None
CHD: Diagnosed
Diabetes: None
Diabetes: Diagnosed
Mobility: 1000+ meters
Mobility: 100+ meters
Mobility: 50−99 meters
Mobility: 5−49 meters
Mobility: Less than 5 meters
Mobility: Did not walk
Hopistalisation: None within the last 90 days
Hopistalisation: 31−90 days ago
Hopistalisation: In the last 30 days
Hopistalisation: Now in hospital
Fatigue: None
Fatigue: Minimal
Fatigue: Moderate
Fatigue: Severe
0.0 0.1 0.2 0.3 0.4 0.5
Population standardized bias (PSB) = abs(exposure group mean − pooled mean) / pooled SD
Unweighted
ITPW

Figure 2


Ordinal regression with and without ITPW
ITPW
Unweighted
DAP−DBI 0−0.99
DAP−DBI 1−2.5
DAP−DBI >2.5
2.53 (1.93−3.31)
1.51 (1.14−2)
2.89 (2.18−3.84)
1.43 (1.09−1.89)
3.67 (2.78−4.85)
2.21 (1.67−2.9)
0
2
4
6
OR of worse cognition outcome
Reference: No exposure